Synthesis of Indoles via Palladium-Catalyzed Annulation of Aryl Chlorides and Internal Alkynes

by

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B. Sc. in Chemistry, University of Massachusetts, Boston, MA
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Department of Chemistry
January 6, 2005

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ABSTRACT

A palladium-catalyzed preparation of 2,3-disubstituted indoles from commercially available and relatively inexpensive reagents, *o*-chloroacetanilide and internal alkynes, is reported. The system is efficient in delivering 2,3-disubstituted indoles in good to excellent yield with a high level of regioselectivity in most cases. Alkynes with alkyl, aryl, alkenyl, and trialkylsilyl substituents are compatible with this methodology.

Thesis Supervisor: Professor Stephen L. Buchwald
Title: Camille Dreyfus Professor of Organic Chemistry

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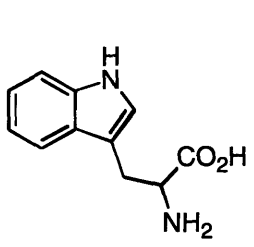
I would like to thank my wife Natalie for her patience, and my son Douglas for his charming lack thereof. I would like to thank my mother for never doubting me. I would like to thank my academic advisor, Professor Stephen L. Buchwald, for his direction and candor during my time at MIT. I would like to thank my fellow group members for their support and assistance; in particular, I am ingratiated to Dr. Peter Tsang for his generous assistance with this thesis. I am indebted to J. R. M. and T. E. B. for many miracles.

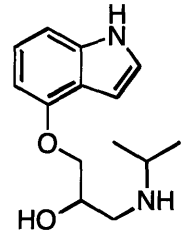
Table of Contents

Introduction

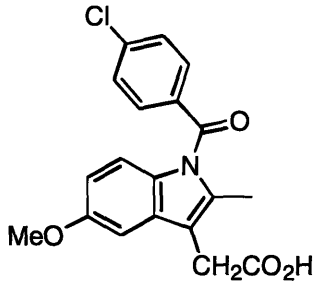
Indole derivatives are one of the most important classes of heterocyclic compounds, owing to their biological activities.[1] The biological significance of 3-(2-aminoethyl)-5-hydroxyindole (serotonin) and tryptophan has motivated the synthesis of thousands of indole-containing pharmaceutical products, such as the β-adrenergic blocker pindolol,[2] and the anti-inflammatory agent indomethacin.[3] The indole moiety is also an



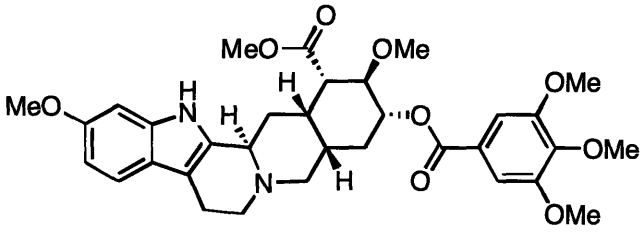
tryptophan



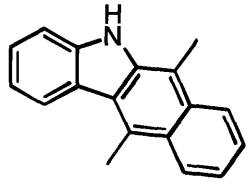
pindolol



indomethacin



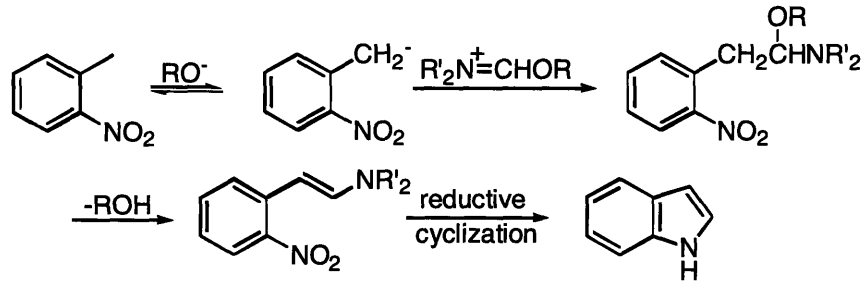
reserpine



ellipticine

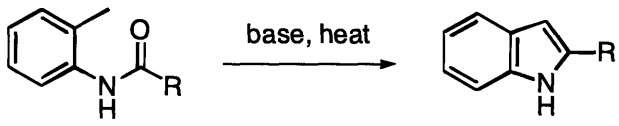
integral component of a variety of alkaloid natural products and antibiotics.[4] For example, reserpine was once used for treating mental disorders,[1] while ellipticine was applied to control tumor activities.[1] The development of convenient and regioselective synthetic protocols for indole and its derivatives continues to be a significant and compelling research objective.[5]

Numerous methods for the preparation of indoles have been developed.[6-11] The Leimgruber-Batcho synthesis,[6] which involves the condensation of an *o*-nitrotoluene with the dimethylacetal of *N,N*-dimethylformamide (Scheme 1), uses relatively simple starting materials. Many functional groups are tolerated, leading to a variety of substituted indoles such as 4-benzyloxy-,[7] 6-chloro-5-methoxy-,[8] and 7-carboxyindole.[9] One major advantage of this method is the regioselective synthesis of indoles which retain the substitution pattern of the *o*-nitrotoluene. Unfortunately, indoles which are substituted at the 2- or 3-positions are inaccessible by this protocol.



Scheme 1. The Leimgruber-Batcho synthesis of indoles.[1]

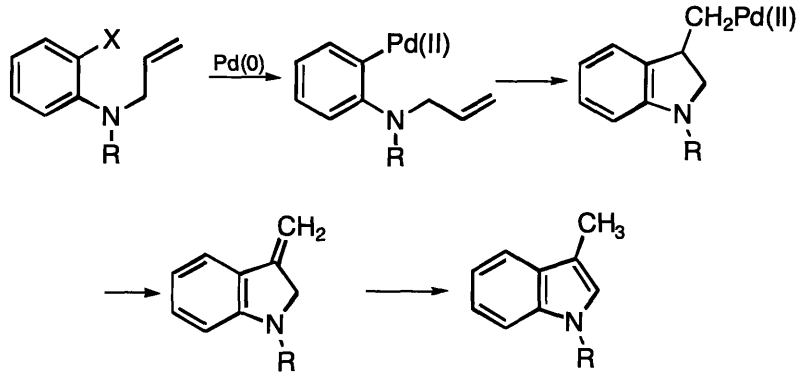
As depicted in Equation 1, the Madelung synthesis can be used to obtain 2-substituted indoles.[10] The use of alkyllithium bases in place of sodium amide allows



(1)

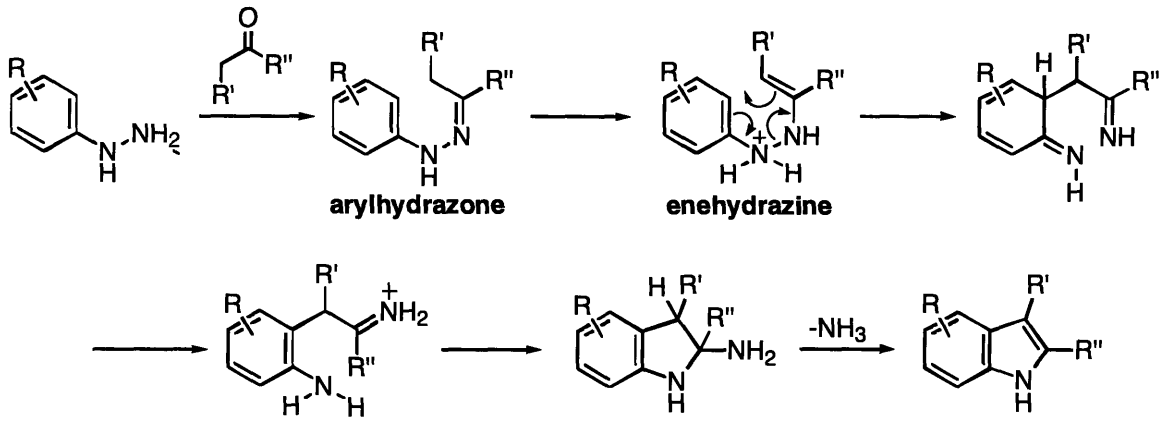
significantly milder reaction conditions to be employed. The Madelung synthesis has limitations in terms of functional group tolerance, although the preparation of 2-halo-, 2-alkyl-, 2-aryl-, and 2-alkenylindoles has been reported.

A particularly interesting metal-catalyzed method for the preparation of indoles, described by Hegedus,[11] can be seen in Scheme 2.[1] An *N*-allyl-*o*-haloaniline cyclizes via an intramolecular Heck reaction to form a 3-substituted indole. The substitution pattern of the substrate is retained in the indole product.



Scheme 2. Synthesis of 3-methylindole by intramolecular Heck reaction.

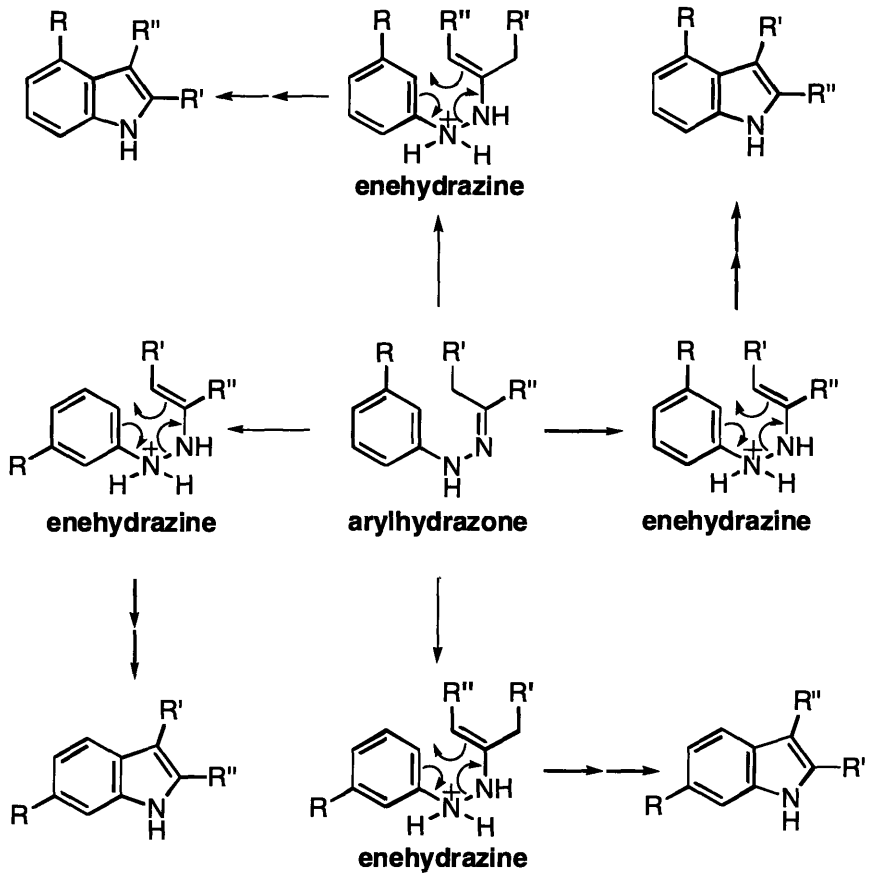
The Fischer indole synthesis has been widely applied to yield indoles substituted in the 2- and/or 3-positions. The indole scaffold is constructed from an arylhydrazine and an aldehyde or ketone. Substituents in the 2- and 3-positions of the indole can be varied by changing the substituents of the carbonyl compound. The reaction is commonly catalyzed under protic conditions or in the presence of Lewis acids. The initial arylhydrazone intermediate tautomerizes to an enehydrazine, which undergoes a sigmatropic rearrangement. The resulting 1,2-disubstituted ring, an imine of an *o*-aminobenzyl ketone, cyclizes and regains aromaticity through the loss of ammonia (Scheme 3). The Fischer synthesis is flexible and tolerates a variety of functional groups,



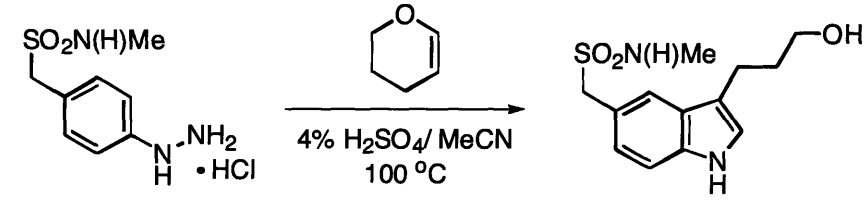
Scheme 3. The Fischer indole synthesis.

which include halogen, hydroxy, alkoxy, ester, and amide groups. Unfortunately, a pair of regioisomeric products is often obtained when the synthesis of 4- or 6-substituted indoles is attempted (Scheme 4). Furthermore, the control of regioselectivity at the 2- and 3-positions is often difficult when unsymmetrical ketones are employed.

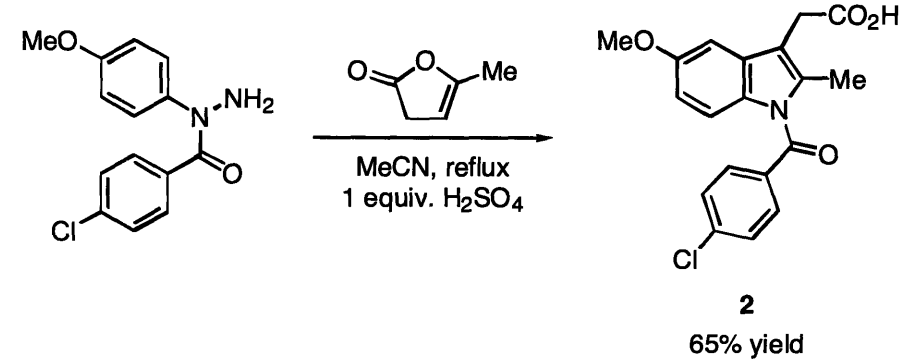
A noteworthy variation of the Fischer synthesis, developed by scientists at Merck,[12] was applied to the assembly of commercial drugs with the indole scaffold. Cyclic enol ethers and enol lactones were employed as synthetic equivalents of aldehyde, and afforded substituted indoles. The use of dihydropyran led to 3-substituted indole **1**, which is a direct precursor to the antimigraine drug sumitriptan (Equation 2). The application of angelicalactone yielded indole acetic acid **2**, the anti-inflammatory agent indomethacin (Equation 3). An increased level of control of 2,3-regioselectivity, relative to the classical Fischer synthesis, was observed, although no discussion of the origin of



Scheme 4. Multiple possible products derived from a single arylhydrazone intermediate.



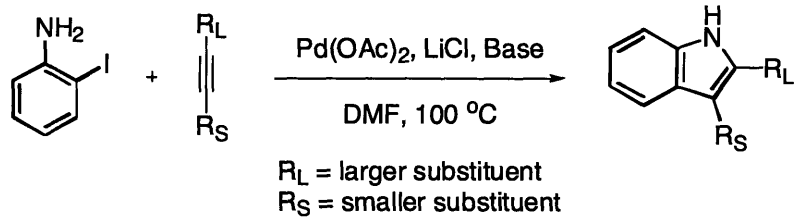
(2)



(3)

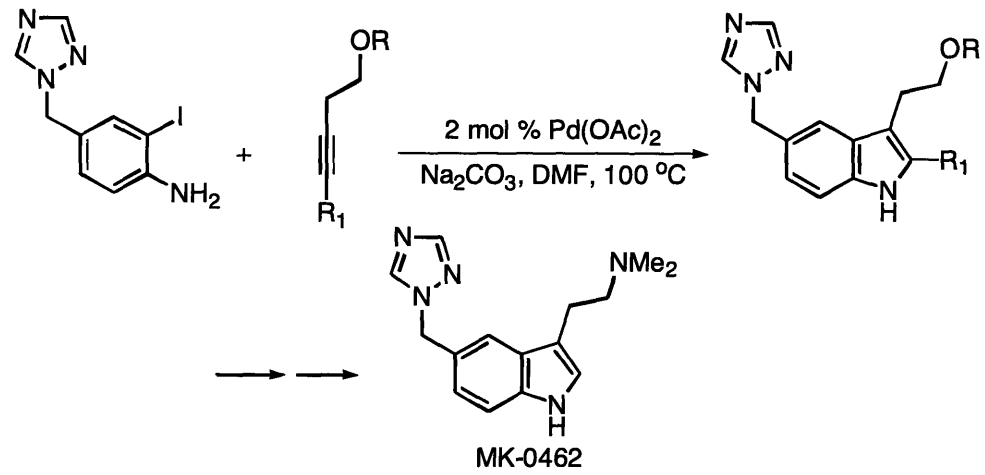
this increased selectivity was presented. Other examples in the same publication suggested that no regiocontrol was observed if a 3-substituted arylhydrazine was employed. Although examples can be found in which regioselectivity was improved by varying catalysts or reaction conditions,[13] a method to prepare indoles which proceeds with total selectivity would be an attractive addition to the range of currently available techniques for indole preparation.

Larock reported a highly regioselective synthesis of indoles via palladium-catalyzed cross-coupling of *o*-iodoaniline and internal alkynes (Equation 4).[14] The



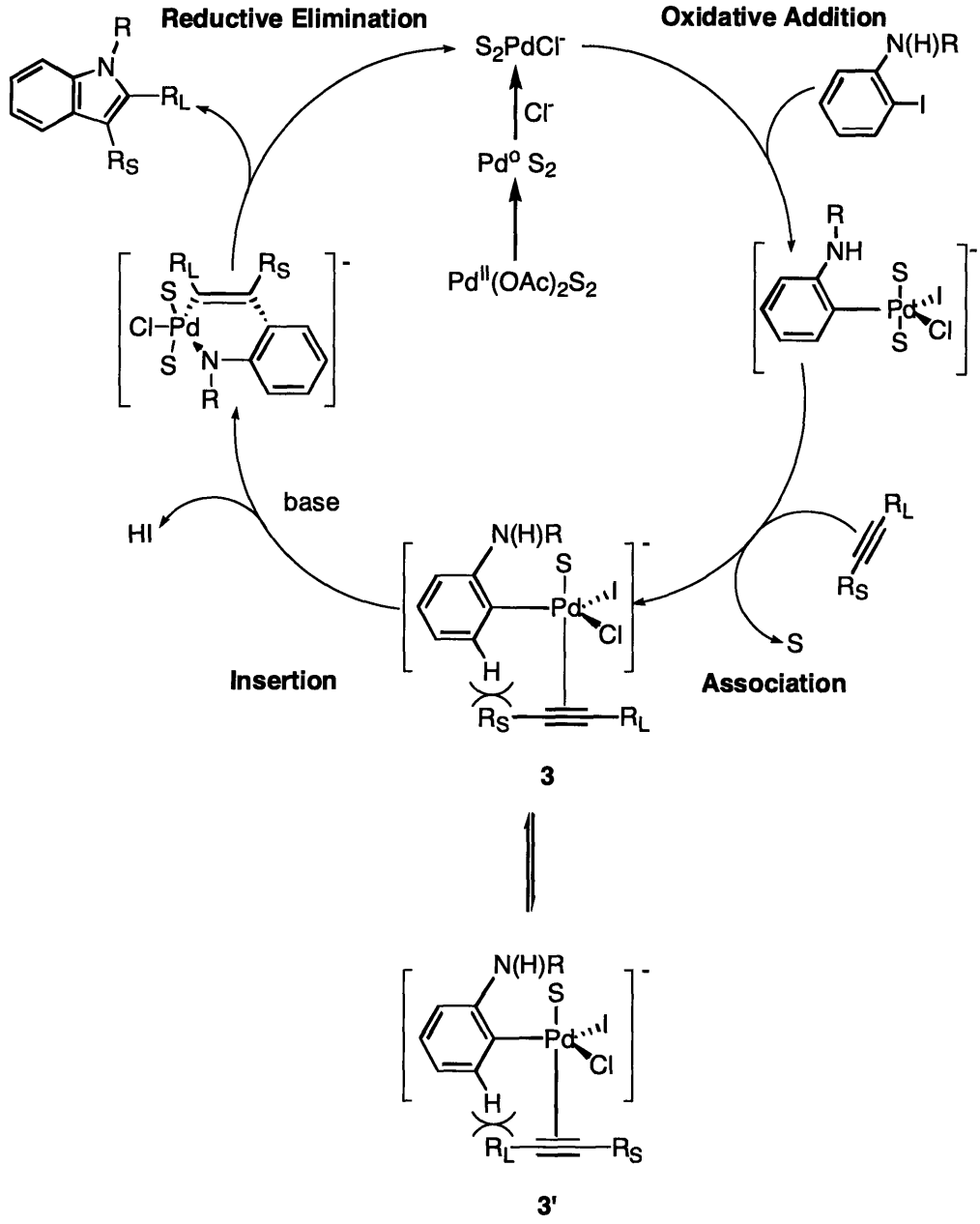
(4)

synthetic protocol tolerates a wide variety of functional groups,[15-17] and has been employed in the large-scale synthesis of the 5-HT_{1D} receptor agonist MK-0462 (Scheme 5).[18]



Scheme 5. Large-scale synthesis of MK-0462.

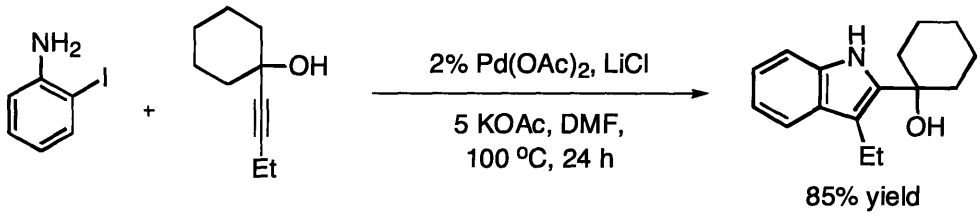
The proposed catalytic cycle for the process is shown in Scheme 6.[14] The reaction begins with oxidative addition of the aryl iodide to a Pd(0) intermediate. This is followed by the association of the alkyne. Insertion of the alkyne into the aryl-palladium bond yields an azapalladacycle, which subsequently undergoes reductive elimination to yield the indole product(s). The insertion of the alkyne into the palladium-carbon bond is the regioselectivity-determining step. The reaction course is dictated by the need to have the larger group of the alkyne become the substituent in the 2-position of the indole. The origin of this regioselectivity is undoubtedly due to the relative stability of **3** versus **3'**.



Scheme 6. The proposed catalytic cycle.

The degree of control of regioselectivity can be illustrated by a few representative examples. Complete regioselectivity was observed when trimethylsilyl-substituted alkynes were used in the synthesis of 2-trimethylsilylindoles. Similarly, propargyl and

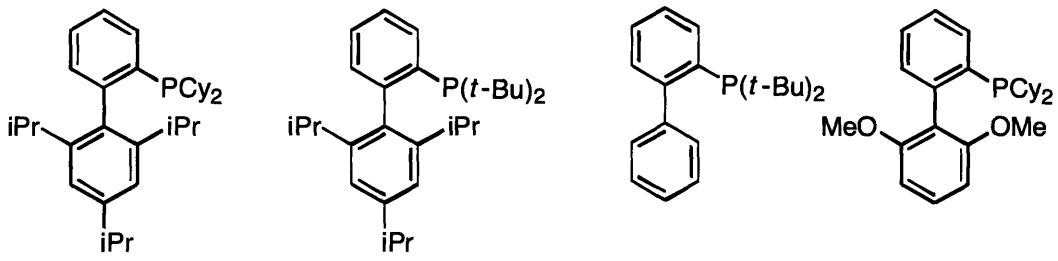
homopropargyl alcohols exclusively gave one regioisomer (Equation 5).



(5)

It appears that the coordination of the oxygen lone pair to palladium also plays an important role in determining the regioselectivity of the indole product. Alkyl-substituted alkynes such as 4,4-dimethyl-2-pentyne and 1-phenylpropyne gave only one of the two possible regioisomers; the product with the larger substituent in the 2-position was observed.

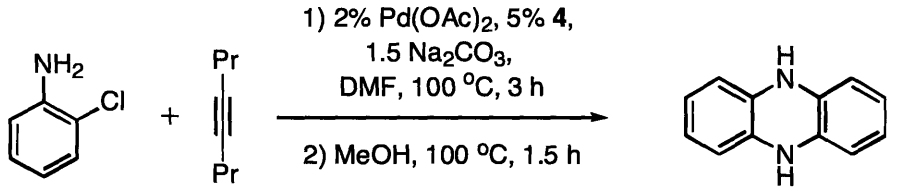
The availability of *o*-iodoanilines is the major drawback of the Larock method. Aryl iodides can be expensive, and the preparation of an *o*-iodoaniline is often complicated by cleavage of the carbon-halide bond as the corresponding nitro compound is reduced. Chloroanilines are less expensive and more readily available. Formation of new carbon-carbon and carbon-nitrogen bonds from aryl chlorides via palladium-catalyzed cross-coupling has recently been achieved by employing bulky biarylphosphine ligands **4-7**.[19] Regioselective synthesis of 2,3-disubstituted indoles from chloroaniline should be possible. In this thesis, we summarize our attempts to access 2,3-disubstituted indoles from chloroaniline substrates. Good yields and regioselectivity are achieved in most cases.



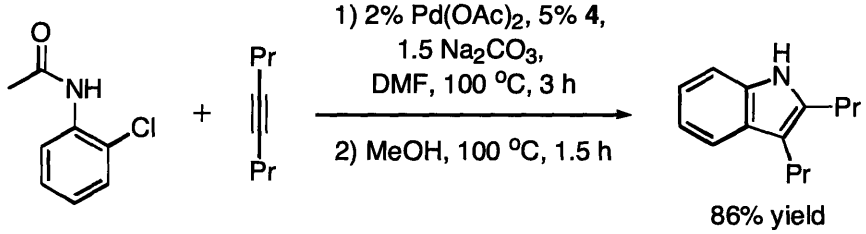
4 **5** **6** **7**

Results and Discussion

Larock's conditions and reagents were applied for initial studies performed by Dr. Xiaolai Zheng. The first successful reaction was achieved in DMF at 100 °C. Attempts to employ free chloroaniline led to a substantial amount of 5,10-dihydrophenazine under both dilute and concentrated conditions (Equation 6). In contrast, *o*-chloroacetanilide gave a good yield of the desired indole product (Equation 7).



5,10-dihydrophenazine (6)



86% yield (7)

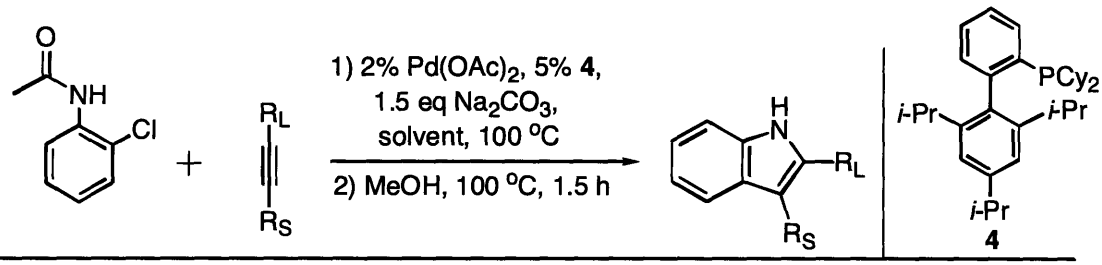
As mentioned above, the annulation reaction was air-sensitive, although purging the reaction vessel with dinitrogen for five minutes was the only required precaution. The reaction was not sensitive to trace amounts of water; the use of oven-dried glassware and/or meticulously dried solvents was unnecessary. The optimal reaction temperature

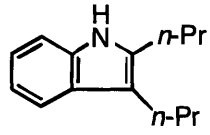
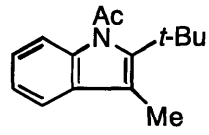
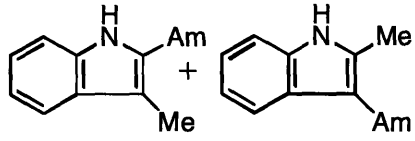
was found to be between 90 and 100 °C. The use of **4** as supporting ligand gave the highest yield of the indole product; the use of other biaryl dialkylphosphine ligands gave much poorer results. The ligand:Pd ratio was critical to the success of the reaction. For example, a ratio of 2.5:1 gave superior results to those obtained at 1:1 or 5:1. Sodium carbonate proved to be a better base than potassium phosphate, cesium carbonate, or triethylamine; 1.5 equiv of base were used.

Screening experiments indicated that DMF was the solvent of choice in many instances. For some other substrates, the use of acetonitrile was superior. For example, the use of acetonitrile gave a significantly improved yield of the indole product when a bulky alkyne, 4,4-dimethylpent-2-yne (*t*-butyl-methylacetylene), was used as the coupling partner. Procedures with other solvents, such as *t*-butyl alcohol, formamide, toluene, or THF, did not give satisfactory yields. A slight excess of alkyne (1.2 equiv) was needed in almost all cases. With highly volatile alkynes, a greater excess was required.

As shown in Table 1, we first examined the reactions of simple alkyl-substituted alkynes. The methanolysis step was not carried out in the reaction between *o*-chloroacetanilide and *t*-butyl-methylacetylene (entry 2, Table 1); the *N*-acetylated indole was obtained. In general, the methanolysis step was omitted in cases where the deprotected indole was difficult to isolate. The same protocol was applied with alkenyl- and aryl-substituted alkyne substrates (Table 2). The regioselectivity observed in Table 2 may result from a combination of both steric and electronic factors.

Table 1. Synthesis of 2,3-dialkyl-substituted indoles.

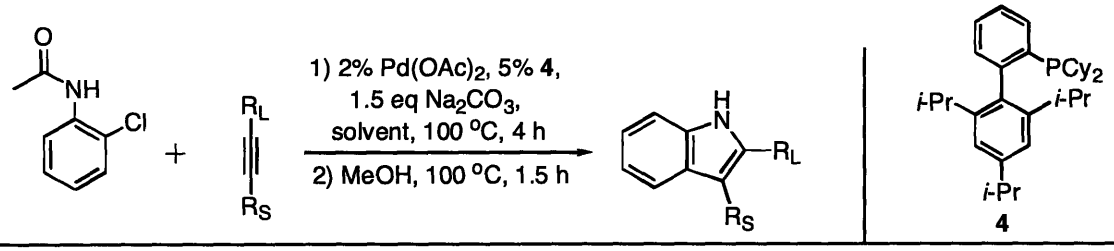


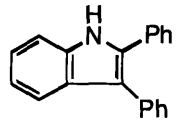
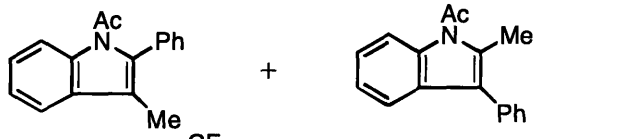
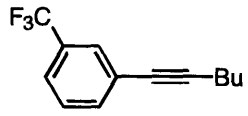
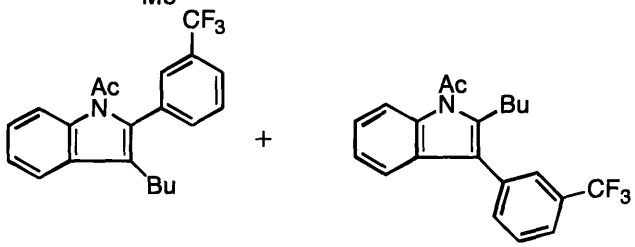
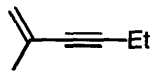
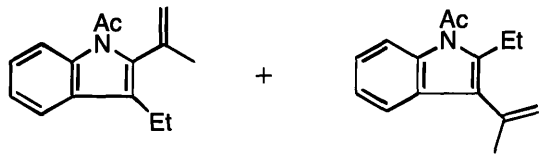
Entry	Alkyne	Reaction Time	Solvent	Indole Product(s)	Yield
1	*n*-Pr—≡—*n*-Pr	3 h	DMF		90%
2	*t*-Bu—≡—Me	9 h	MeCN		78%
3	Am—≡—Me	3.5 h	DMF		76%[a]

a. This is a combined yield; regioisomeric ratio was approximately 1:1.

In terms of regioselectivity, the only case in which our results differed substantially from Larock's was that of 1-phenyl-1-propyne (entry 2, Table 2). Unlike his report, we did not observe the exclusive formation of 3-methyl-2-phenyl-1*H*-indole. Instead, a pair of regioisomers was observed.

Table 2. Synthesis of alkenyl- and aryl-substituted indoles.



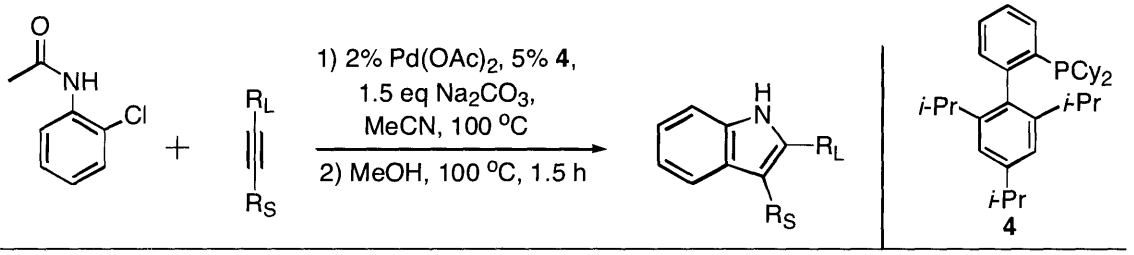
Entry	Alkyne	Indole Product(s)	Yield
1	Ph—≡—Ph		89%
2[a]	Ph—≡—Me		88%[b]
3			78%[b]
4			90%[c]

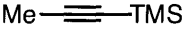
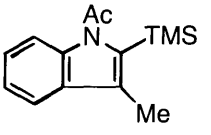
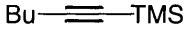
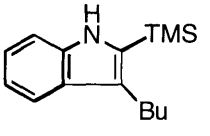
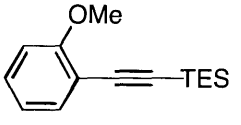
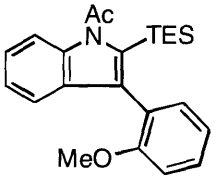
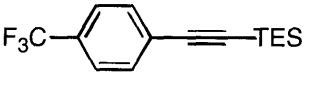
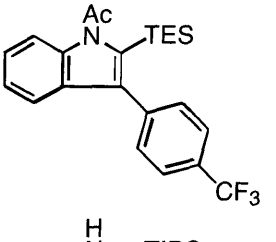
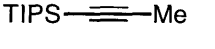
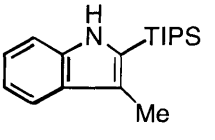
DMF was the solvent unless otherwise stated. a. The reaction was run in MeCN. b. This is a combined yield; the regioisomeric ratio was 6:1. c. This is a combined yield; the regioisomeric ratio was 7:1.

Another class of alkynes employed was the trialkylsilyl-substituted alkynes (Table 3). The ability of the bulky trialkylsilyl groups in directing regiochemistry in our system, and the ease of subsequent protonolysis of these silyl groups,[14] makes these alkynes particularly attractive in accessing 2-*H*-3-substituted indoles. These 2-*H*-3-substituted indoles can be further derivatized to yield 2-halo-3-substituted indoles, or 2-

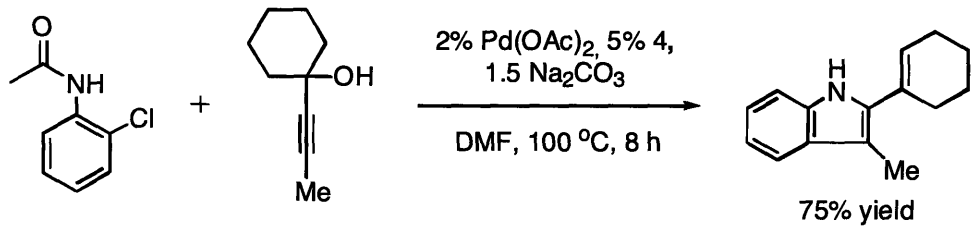
(1-alkenyl)indoles.[20]

Table 3. Synthesis of 2-trialkylsilyl-substituted indoles.



Entry	Alkyne	Reaction Time	Indole Product	Yield
1		9 h		86%
2		9 h		79%
3		22 h		76%
4		14 h		82%
5		24 h		72%

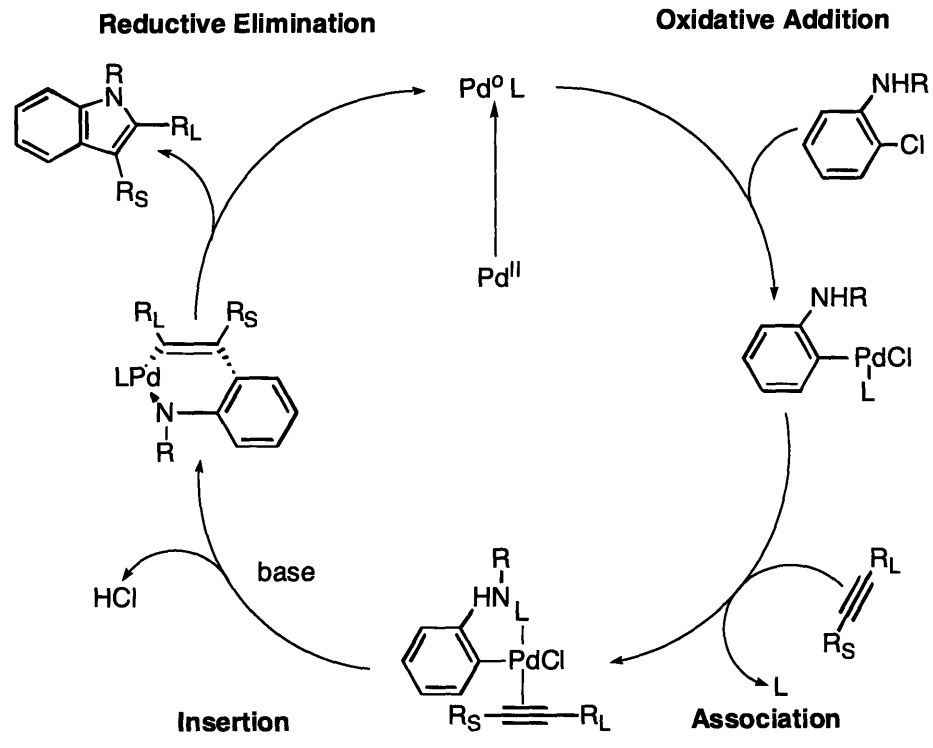
A final class of substrates studied was propargyl alcohols. The primary alcohol 2-butynol was unreactive. The tertiary alcohol 1-prop-1-ynyl-cyclohexanol gave a deacetylated indole in 75% yield without applying methanolysis (Equation 8). The



(8)

product presumably was formed via acyl transfer from the nitrogen to the hydroxy group,[14] followed by elimination of the acetate ion.

A catalytic cycle for our system is proposed. As shown in Scheme 7, the reaction begins with an oxidative addition step, followed by association, insertion, and reductive elimination steps. The effects of the bulky biaryl ligand on the structures of intermediates are not well understood at this point. Understanding the structures of these intermediates may lead to insights for future design of protocols in regioselective synthesis of 2,3-disubstituted indoles.



Scheme 7. The proposed catalytic cycle for our system. Solvent molecules are omitted.

Conclusions

We have developed a palladium-catalyzed preparation of 2,3-disubstituted indoles from commercially available and relatively inexpensive *o*-chloroacetanilide and internal alkynes. The system is efficient in delivering 2,3-disubstituted indoles in good to excellent yield with a high level of regioselectivity in most cases. Alkynes with alkyl, aryl, alkenyl, and trialkylsilyl substituents are compatible with this methodology.

Experimental Section

General. All reactions were conducted in dry glassware under an inert atmosphere of dinitrogen. Commercially available chemicals were obtained from Aldrich Chemical Co. and Lancaster Synthesis. Palladium acetate was obtained from

Engelhard Industries. Solid reagents were used as received and weighed under air. Liquid reagents were distilled prior to use. Anhydrous DMF and acetonitrile were purchased in Sure-Seal bottles and used as received.

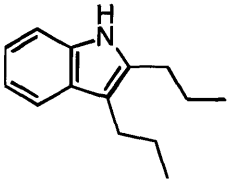
Infrared (IR) spectra were recorded on an ASI REACTIR® 1000 instrument by placing neat or solution samples on the DiComp probe; ν_{max} data were reported in cm^{-1}. Nuclear magnetic resonance (NMR) spectra were recorded at 20 °C on a Varian 500 MHz instrument. Chemical shifts were reported in ppm from tetramethylsilane (TMS). Gas chromatographic (GC) analyses were performed on Agilent 6890 instruments. Melting points were uncorrected, and recorded on a MelTemp from Laboratory Devices, Inc. Preparative flash chromatography was performed with EMD silica gel (230-400 mesh). Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA. Yields reported refer to isolated yields (an average of at least two runs) of compounds estimated to be at least 95% pure as determined by ^{1}H and ^{13}C NMR, and combustion analysis.

Representative procedures for heteroannulation of internal alkynes with *o*-chloroacetanilide (procedure A). Palladium acetate (2.2 mg, 0.01 mmol, 2.0 mol %), **4** (11.9 mg, 0.025 mmol, 5.0 mol %), *o*-chloroacetanilide (84.8 mg, 0.5 mmol), and anhydrous sodium carbonate (159 mg, 1.5 mmol) were loaded into a Schlenk tube under air. The Schlenk tube was evacuated and refilled with dinitrogen; this evacuation-refill cycle was repeated one additional time. Under a positive pressure of dinitrogen, 1-trimethylsilyl-1-hexyne (121 μL, 0.6 mmol) and acetonitrile (2 mL) were added via syringe. The Schlenk tube was sealed with a teflon screw cap, and the reaction mixture

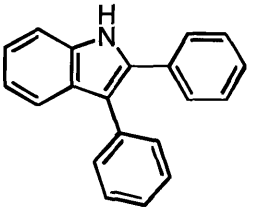
was stirred in an oil bath at 100 °C for 9 h. The reaction mixture was cooled to room temperature, and methanol (4 mL) was added. The Schlenk tube was resealed and heated in an oil bath at 100 °C for an additional 1.5 h. The reaction mixture was cooled to room temperature, and filtered through a pad of Celite. Silica gel (1.5 g) was added to the filtrate and volatiles were removed with the aid of a rotary evaporator. The solid residue was loaded on top of a silica gel column for purification by flash chromatography (9:1 hexanes:Et_2O). A pale yellow oil of 2-trimethylsilyl-3-butylindole (97 mg, 79%) was obtained by concentration of the appropriate fractions. It should be noted that the methanolysis step can be omitted to yield the corresponding *N*-acetylated indole.

Representative procedures for heteroannulation of internal alkynes with *o*-chloroacetanilide (procedure B). Palladium acetate (2.2 mg, 0.01 mmol, 2.0 mol %), **4** (11.9 mg, 0.025 mmol, 5.0 mol %), *o*-chloroacetanilide (84.8 mg, 0.5 mmol), and anhydrous sodium carbonate (159.0 mg, 1.5 mmol) were loaded into a 10 mL disposable tube under air. The tube was tightly sealed with a screw cap fitted with a teflon septum and vigorously purged with dinitrogen for 5 min. Liquid reagents, 4-octyne (88 μL, 0.6 mmol) and *N,N*-dimethylformamide (2 mL), were added via syringe. The reaction mixture was stirred in an oil bath at 100 °C for 3 h. The tube was removed from the oil bath, and methanol (4 mL) was carefully added to it while its contents were still hot. It is recommended that the tube be allowed to cool before addition of methanol. The tube was resealed with a fresh teflon septum, and the reaction mixture was stirred at 100 °C for an additional 1.5 h. The reaction mixture was cooled to room temperature, and transferred to a round-bottom flask. Volatiles were removed with the aid of a rotary evaporator. The

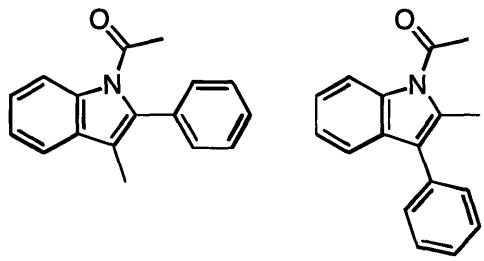
remaining solution was washed with water (10 mL) and extracted with ethyl ether (3 x 10 mL). Silica gel (1.5 g) was added to the combined organic fractions, and the heterogeneous mixture was concentrated with the aid of a rotary evaporator to yield a greenish-brown powder; this was subsequently purified by flash chromatography (9:1 hexanes:Et_2O). A pale yellow oil of 2,3-dipropylindole (92 mg, 90%) was obtained by concentration of the appropriate fractions. It should be noted that the methanolysis step can be omitted to yield the corresponding *N*-acetylated indoles. In this case, one can proceed directly to the washing/extraction step from the completed reaction.



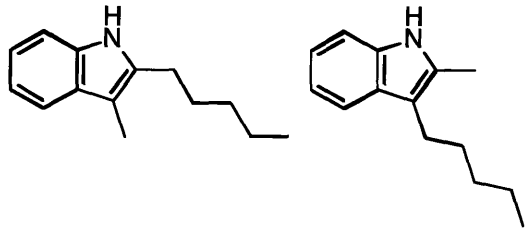
2,3-dipropyl-1*H*-indole was prepared as described in procedure B. ^1H and ^{13}C NMR spectra were identical to those previously reported.[14]



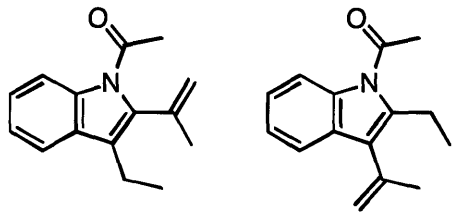
2,3-diphenyl-1*H*-indole was prepared as described in procedure B, with the reaction time lengthened to 6 h. The purified compound was obtained as a white solid (120 mg, 89%), m.p.: 113-115 °C (Lit.[21] 114-116 °C). ^1H and ^{13}C NMR spectra were identical to those previously reported.[21]



1-(3-methyl-2-phenyl-indol-1-yl)-ethanone and **1-(2-methyl-3-phenyl-indol-1-yl)-ethanone** were prepared as described in procedure A. The reaction time was 4 h, and the methanolysis step was not carried out. Flash chromatography of the crude mixture enabled separation of the two regioisomers, with a combined yield of 88%. The major regioisomer was 1-(3-methyl-2-phenyl-indol-1-yl)-ethanone; the isomeric ratio was 6:1. The major isomer was obtained as a white solid (91 mg, 73%), m.p.: 80-81 °C (Lit.[14] 80.5-81.5 °C). The minor isomer was also a white solid (18 mg, 15%), m.p.: 116-118 °C. ^{1}H and ^{13}C NMR spectra of the major regioisomer were identical to those previously reported.[14] Characterization data for the minor regioisomer: IR ($CHCl_3$): 3160, 3129, 2932, 1701, 1660 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.63 (s, 3 H), 2.81 (s, 3 H), 7.24-7.52 (m, 8 H), 8.05 (d, 1 H, J = 8.54 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.58, 27.93, 115.34, 119.33, 119.46, 120.46, 122.80, 123.53, 124.39, 127.49, 128.84, 130.25, 130.42, 133.40, 133.74, 135.98, 170.83. Anal. Calcd. for $C_{17}H_{15}NO$: C, 81.90; H, 6.06. Found: C, 81.81; H, 6.12.

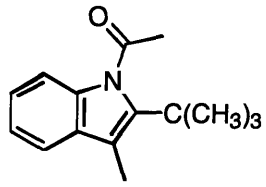


3-methyl-2-pentyl-1*H*-indole and **2-methyl-3-pentyl-1*H*-indole** were prepared as described in procedure B. Flash chromatography of the crude mixture enabled separation of the two regioisomers, with a combined yield of 76%. The major regioisomer was 3-methyl-2-pentyl-1*H*-indole; the isomeric ratio was 1.1:1. The major isomer was obtained as a pale yellow oil (40 mg, 40%). The minor isomer was also a pale yellow oil (35 mg, 36%). Characterization data for the major regioisomer: IR ($CHCl_3$): 3401, 3109, 2955, 1659 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.91-0.97 (m, 3 H), 1.35-1.41 (m, 4 H), 1.66-1.70 (m, 2 H), 2.24 (s, 3 H), 2.74 (t, 2 H, J = 7.63 Hz), 7.12-7.14 (m, 2 H), 7.29 (d, 1 H, J = 7.22 Hz), 7.53 (d, 1 H, J = 7.34 Hz), 7.68 (br s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.7, 14.2, 22.9, 26.4, 29.8, 31.5, 107.1, 110.2, 118.2, 119.1, 121.1, 129.7, 135.5, 135.8. Characterization data for the minor regioisomer: IR ($CHCl_3$): 3389, 3145, 2933, 1655 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.90-0.94 (m, 3 H), 1.33-1.41 (m, 4 H), 1.62-1.68 (m, 2 H), 2.40 (s, 3 H), 2.71 (t, 2 H, J = 7.63 Hz), 7.08-7.14 (m, 2 H), 7.27 (d, 1 H, J = 7.62 Hz), 7.54 (d, 1 H, J = 8.24 Hz), 7.66 (br s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.9, 14.4, 22.8, 24.2, 30.7, 32.0, 110.3, 112.8, 118.4, 119.1, 121.0, 129.1, 130.8, 135.3.

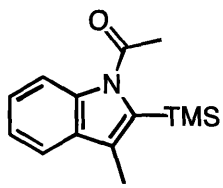


1-(3-ethyl-2-isopropenyl-indol-1-yl)-ethanone and **1-(2-ethyl-3-isopropenyl-indol-1-yl)-ethanone** were prepared as described in procedure B. The reaction time was 4 h, and the methanolysis step was not carried out. Flash chromatography of the crude mixture afforded a mixture of regioisomers as a pale yellow oil. The yield was 102 mg (90%). ^{1}H NMR indicated a product ratio of approximately 5:1, with 1-(3-ethyl-2-isopropenyl-indol-1-yl)-ethanone as the major product. Characterization data for the mixture: IR ($CHCl_3$): 3160, 3144, 2927, 1700, 1681, 1653 cm^{-1}. The following resonances refer to the major isomer, and were taken from the ^{1}H NMR spectrum of the mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (t, 3 H, J = 7.62 Hz), 2.10 (s, 3 H), 2.68 (s, 3 H), 2.70-2.75 (q, 2 H, J = 7.62 Hz), 5.22-5.28 (m, 1 H), 5.48-5.44 (m, 1 H), 7.23-7.38 (m, 2 H), 7.56 (d, 1 H, J = 7.63 Hz), 8.31 (d, 1 H, J = 8.24 Hz). The following resonances refer to the minor isomer, and were taken from the ^{1}H NMR spectrum of the mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.15 (s, 0.38 H), 2.82 (s, 0.48 H), 3.07-3.13 (q, 0.29 H, J = 7.62 Hz), 5.05-5.09 (m, 0.18 H), 5.42-5.46 (m, 0.17 H), 7.51 (d, 0.19 H, J = 7.63 Hz), 7.81 (d, 0.18 H, J = 8.24 Hz). The following resonances refer to the major isomer, and were taken from the ^{13}C NMR spectrum of the mixture: ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.6, 18.1, 24.9, 26.7, 118.0, 119.8, 119.9, 124.6, 125.9, 130.6, 133.3, 137.6, 203.5. The following resonances refer to the minor isomer, and were taken from the ^{13}C NMR spectrum of the mixture: ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 24.6, 28.9, 29.3, 107.3, 115.4, 118.8, 120.5, 122.0, 123.8, 129.9, 137.5, 171.5. Anal. Calcd. for $C_{15}H_{17}NO$:

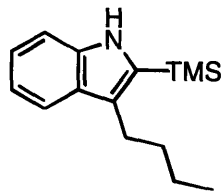
C, 79.26; H, 7.54. Found: C, 79.04; H, 7.69.



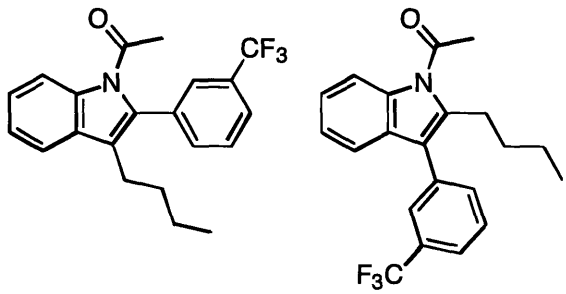
1-(2-*tert*-butyl-3-methyl-indol-1-yl)-ethanone was prepared as described in procedure A, except that 2 equiv of the alkyne were used. The reaction time was 13 h, and the methanolysis step was not carried out. Flash chromatography of the crude product afforded a pale yellow oil (89 mg, 78%). IR ($CHCl_3$): 3144, 2979, 2932, 1706, 1659 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.48-1.54 (m, 9 H), 2.42 (s, 3 H), 2.76 (s, 3 H), 7.10-7.52 (m, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.1, 28.7, 30.4, 31.4, 35.3, 112.5, 117.3, 119.2, 122.7, 124.3, 132.9, 136.5, 146.4, 176.6. Anal. Calcd. for $C_{15}H_{19}NO$: C, 78.56; H, 8.45. Found: C, 78.72; H, 8.83.



1-(3-methyl-2-trimethylsilanyl-indol-1-yl)-ethanone was prepared as described in procedure A, except that 2 equiv of the alkyne were used. The reaction time was 9 h, and the methanolysis step was not carried out. Flash chromatography of the crude product afforded a white solid (113 mg, 92%), m.p.: 64-66 °C (Lit.[14] 65-67 °C). ^1H and ^{13}C NMR spectra were identical to those previously reported.[14]

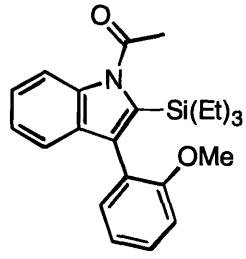


3-butyl-2-trimethylsilanyl-1H-indole was prepared as described in procedure A. ^{1}H and ^{13}C NMR spectra were identical to those previously reported.[14]



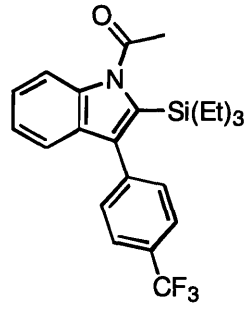
1-[3-butyl-2-(3-trifluoromethyl-phenyl)-indol-1-yl]-ethanone and **1-[2-butyl-3-(3-trifluoromethyl-phenyl)-indol-1-yl]-ethanone** were prepared as described in procedure B. The reaction time was 4 h, and the methanolysis step was not carried out. Flash chromatography of the crude mixture afforded a mixture of regioisomers as a pale yellow oil. The yield was 140 mg (78%). ^{1}H NMR indicated a product ratio of approximately 6:1, with 1-[3-butyl-2-(3-trifluoromethyl-phenyl)-indol-1-yl]-ethanone as the major product. Characterization data for the mixture: IR ($CHCl_3$): 3155, 3141, 2960, 2931, 1706, 1665 cm^{-1}. The following resonances refer to the major isomer, and were taken from the ^{1}H NMR spectrum of the mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, 3 H, J = 7.63 Hz), 1.31-1.35 (m, 2 H), 1.59-1.65 (m, 2 H), 2.04 (s, 3 H), 2.57 (t, 2 H, J = 7.94 Hz), 7.35-7.46 (m, 2 H), 7.61-7.68 (m, 3 H), 7.72-7.78 (m, 2 H), 8.44 (d, 1 H, J = 8.24 Hz). The following resonances refer to the minor isomer, and were taken from the

^{1}H NMR spectrum of the mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (t, 0.66 H, J = 7.63 Hz), 1.46-1.50 (m, 0.53 H), 1.73-1.79 (m, 0.63 H), 2.87 (s, 0.56 H), 2.92 (t, 0.47 H), 7.18-7.31 (m, 0.43 H), 7.68-7.72 (m, 0.69 H), 7.85-7.89 (m, 0.51 H). The following resonances refer to the major isomer, and were taken from the ^{13}C NMR spectrum of the mixture: ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 23.0, 24.3, 27.4, 28.1, 28.3, 111.8, 115.4, 120.4, 120.6, 124.2, 126.1, 126.1, 127.8, 127.8, 130.2, 130.4, 132.1, 134.0, 171.6. The following resonances refer to the minor isomer, and were taken from the ^{13}C NMR spectrum of the mixture: ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 22.9, 23.3, 24.7, 32.8, 33.1, 117.3, 120.1, 123.6, 124.5, 125.1, 126.6, 130.1, 130.2, 132.3, 134.5, 135.6, 138.0. Anal. Calcd. for $C_{21}H_{20}F_3NO$: C, 70.18; H, 5.61. Found: C, 70.48; H, 5.81.

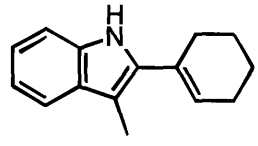


1-[3-(2-methoxy-phenyl)-2-triethylsilanyl-indol-1-yl]-ethanone was prepared as described in procedure A. The reaction time was 22 h, and the methanolysis step was not carried out. Flash chromatography of the crude product afforded a white solid (144 mg, 76%), m.p.: 112-114 °C. IR ($CHCl_3$): 3126, 2962, 1711, 1625, 1116 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.56-0.64 (m, 6 H), 0.83 (t, 9 H, J = 7.93 Hz), 2.89 (s, 3 H), 3.74 (s, 3 H), 6.98-7.04 (m, 2 H), 7.14-7.23 (m, 3 H), 7.31-7.35 (m, 1 H), 7.41-7.44 (m, 1 H), 7.70 (d, 1 H, J = 8.24 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 5.1, 7.9, 26.9, 55.2, 110.4,

113.5, 120.9, 121.9, 123.4, 125.1, 125.6, 130.3, 133.1, 133.9, 134.5, 137.0, 137.6, 158.8, 170.3. Anal Calcd. for $C_{23}H_{29}NO_2Si$: C, 72.78; H, 7.70. Found: C, 72.93; H, 7.62.

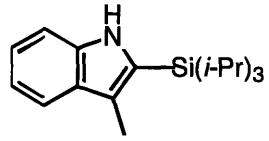


1-[2-triethylsilanyl-3-(4-trifluoromethyl-phenyl)-indol-1-yl]-ethanone was prepared as described in procedure A. The reaction time was 14 h, and the methanolysis step was not carried out. Flash chromatography of the crude product afforded a white solid (171 mg, 82%), m.p.: 108-110 °C. IR ($CHCl_3$): 3131, 2936, 1685, 1653. ^1H NMR (500 MHz, $CDCl_3$) δ 0.59 (q, 6 H, J = 8.24 Hz), 0.83 (t, 9 H, J = 7.93 Hz), 2.91 (s, 3 H), 7.23 (d, 2 H, J = 3.97), 7.36-7.42 (m,1 H), 7.53 (d, 2 H, J = 7.94), 7.68-7.76 (m, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ -17.2, 5.4, 8.4, 27.1, 114.5, 121.2, 123.8, 125.8, 126.1, 132.0, 133.9, 136.8, 137.6, 171.0. Anal. Calcd. for $C_{23}H_{26}F_3NOSi$: C, 66.16; H, 6.28. Found: C, 66.26; H, 6.34.

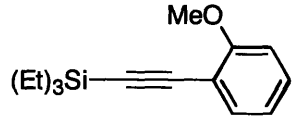


2-Cyclohex-1-enyl-3-methyl-1*H*-indole was prepared as described in procedure B. The reaction time was 8 h, and the methanolysis step was not carried out. Flash chromatography of the crude product afforded a colorless oil (86 mg, 75%). IR ($CHCl_3$):

3423, 3128, 3111, 2960, 2913, 1628 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.71-1.77 (m, 2 H), 1.79-1.85 (m, 2 H), 2.26-2.32 (m, 2 H), 2.40 (s, 3 H), 2.44-2.50 (m, 2 H), 6.05-6.09 (m, 1 H), 7.10-7.18 (m, 2 H), 7.29 (d, 1 H, J = 7.93 Hz), 7.55 (d, 1 H, J = 7.93 Hz), 7.82 (br s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) 10.4, 22.4, 23.2, 26.0, 28.3, 107.9, 111.1, 119.3, 120.0, 122.5, 128.2, 131.0, 130.9, 135.8, 136.9.

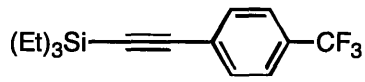


3-Methyl-2-(triisopropyl-silanyl)-1*H*-indole was prepared as described in procedure A. The reaction time was 24 h. Flash chromatography of the crude product afforded colorless crystals (104 mg, 72%), m.p.: 85-86 °C. IR ($CHCl_3$): 3404, 3129, 2942, 1626 cm-1. ^1H NMR (500 MHz, $CDCl_3$) δ 1.16 (d, 18 H, J = 7.32 Hz), 1.50 (septet, 3 H, J = 7.32 Hz), 2.44 (s, 3 H), 7.09-7.15 (m, 1 H), 7.17-7.23 (m, 1 H), 7.36 (d, 1 H, J = 7.93 Hz), 7.61 (d, 1 H, J = 7.93 Hz), 7.91 (br s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.4, 12.2, 18.9, 111.4, 119.5, 119.6, 121.9, 122.9, 129.1, 129.8, 137.6. Anal. Calcd. for $C_{18}H_{29}NSi$: C, 75.19; H, 10.17. Found: C, 75.17; H, 10.17.

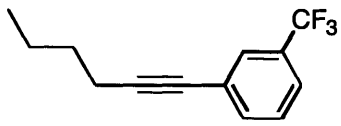


Triethyl-(2-methoxy-phenylethynyl)-silane was prepared from triethylsilylacetylene and 2-chloroanisole following a published procedure.[19b] The reaction scale was 5 mmol. The reaction mixture was stirred at 90 °C for 2.5 h. Flash chromatography of the crude product afforded a yellow oil (1.047 g, 85%). IR ($CHCl_3$):

3133, 2967, 1785, 1632, 1125 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.70 (q, 6 H, J = 7.93 Hz), 1.08 (t, 9 H, J = 7.94 Hz), 3.87 (s, 3 H), 6.85-6.90 (m, 2 H), 7.25-7.31 (m, 1 H), 7.42-7.48 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.8, 7.8, 56.3, 96.7, 103.3, 107.3, 111.5, 113.4, 121.2, 130.8, 135.0. Anal. Calcd. for $C_{15}H_{22}OSi$: C, 73.11; H, 9.00. Found: C, 73.27; H, 9.22.



Triethyl-(4-trifluoromethyl-phenylethynyl)-silane was prepared from triethylsilylacetylene and chloro-4-trifluoromethylbenzene following a published procedure.[19b] The reaction scale was 5 mmol. The reaction mixture was stirred at 70 °C for 2 h. Flash chromatography of the crude product afforded a yellow oil (1.364 g, 96%). IR ($CHCl_3$): 3187, 2929, 1685 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.71 (q, 6 H, J = 7.94 Hz), 1.35 (t, 9 H, J = 7.93 Hz), 7.53-7.61 (m, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.5, 7.7, 95.5, 105.5, 123.7, 126.0, 128.0, 131.1, 133.2. Anal. Calcd. for $C_{15}H_{19}F_3Si$: C, 63.35; H, 6.73. Found: C, 63.21; H, 6.80.



1-Hex-1-ynyl-3-trifluoromethyl-benzene was prepared from 1-hexyne and chloro-3-trifluoromethylbenzene following a published procedure.[19b] The reaction scale was 5 mmol. The reaction mixture was stirred at 70 °C for 2 h. Flash chromatography of the crude product afforded a colorless oil (1.040 g, 92% yield). ^1H and ^{13}C NMR spectra were identical to those previously reported.[22]

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APPENDIX:

Selected Spectra

STANDARD PROTON PARAMETERS

exp1 s2pul

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tn	H1	dseq	
at	3.277	dres	1.0
np	65536	homo	n
sw	9998.8	DEC2	
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pw	8.2	dof2	0
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hs	nn	dof3	0
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vs	151	dseq3	
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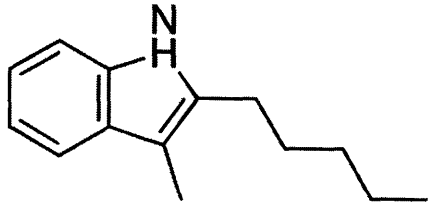
nm cdc ph		werr	
		wexp	
		wbs	
		wnt	



STANDARD CARBON PARAMETERS

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gain	not used	DEC3	
FLAGS		dfrq3	0
il	n	dn3	
in	n	dpwr3	1
dp	y	dof3	0
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DISPLAY		dmm3	c
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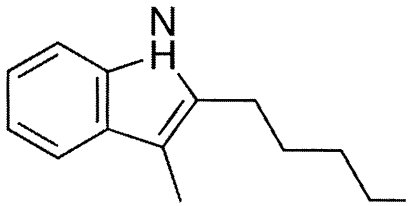
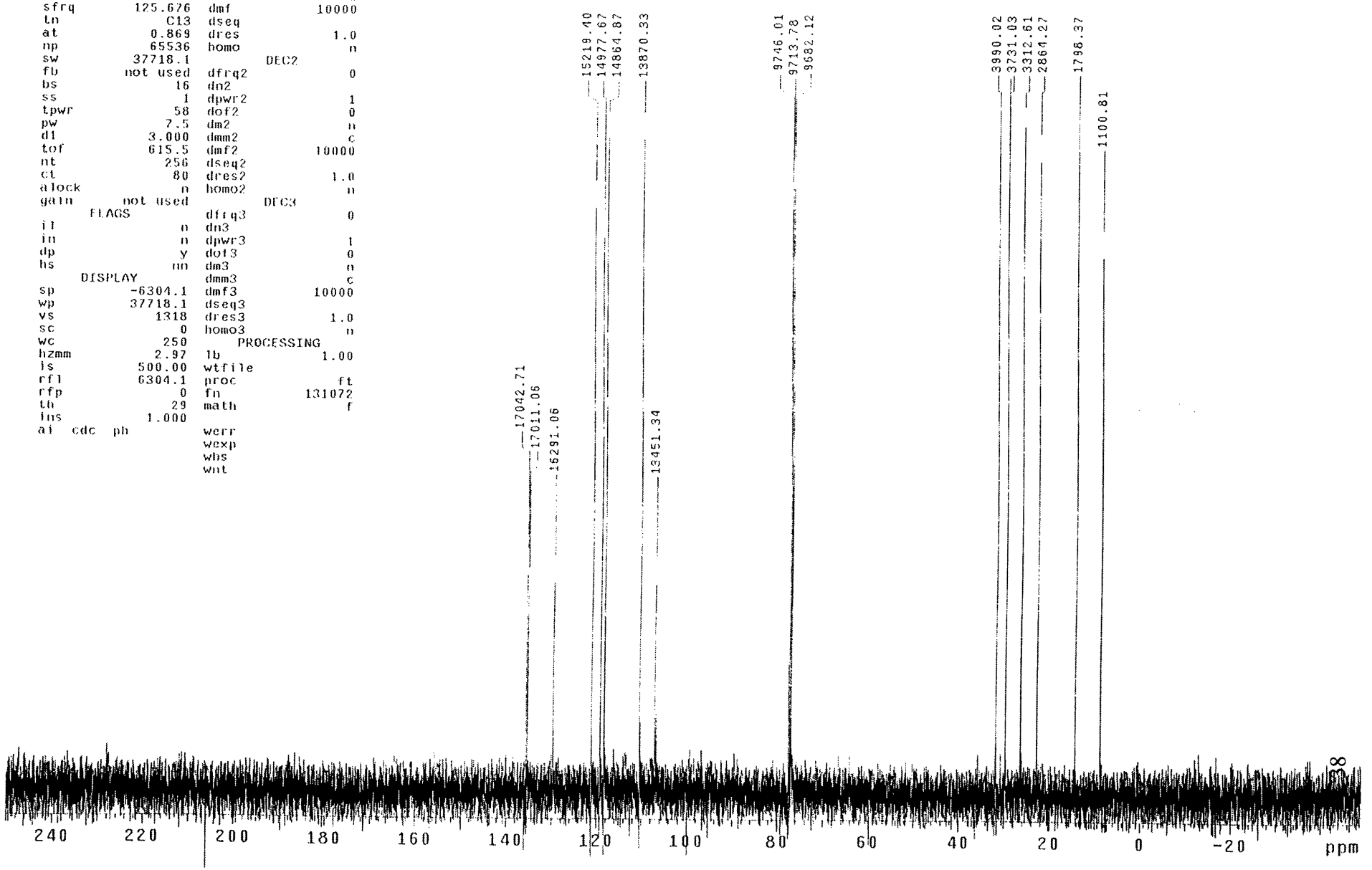
		wnt	





STANDARD PROTON PARAMETERS

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ACQUISITION		dmm	w
sfrq	499.758	dmf	10000
tn	H1	dseq	
at	3.277	dres	1.0
np	65536	homo	n
sw	9998.8	DEC2	
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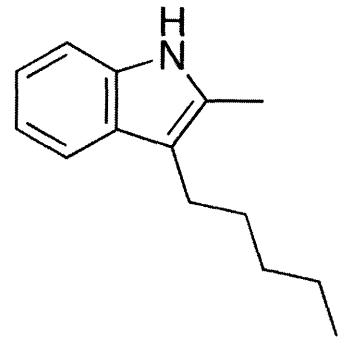

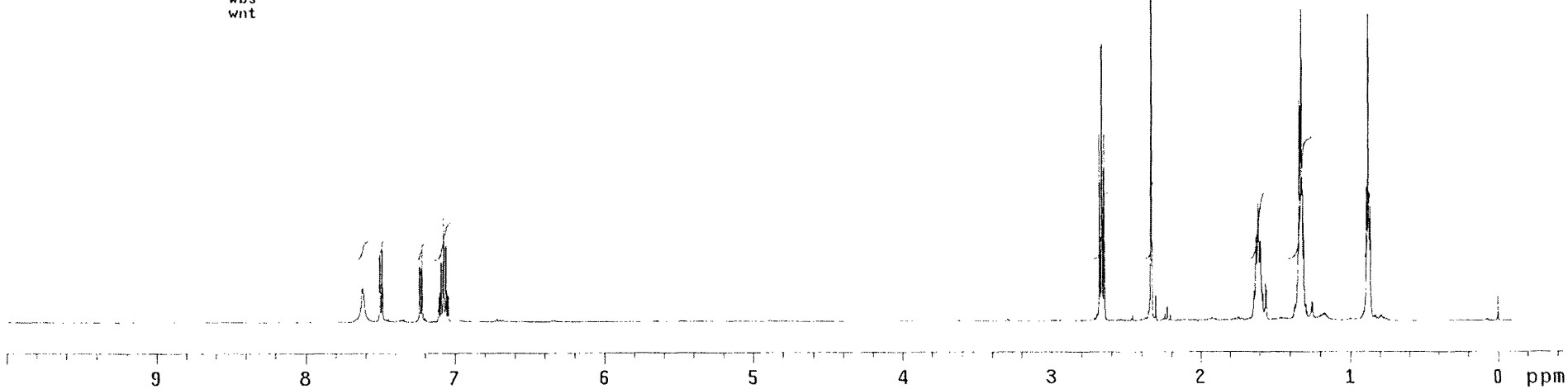


STANDARD CARBON PARAMETERS
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tpwr 58
pw 7.5
d1 3.000
tof 615.5
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gain n
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20
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ppm

STANDARD PROTON PARAMETERS

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ACQUISITION		dmf	10000
sfrq	499.758	dseq	
tn	H1	dres	1.0
at	3.277	homo	n
np	65536	DEC2	
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ct	8	dres2	1.0
alock	n	homo2	n
gain	not used	DEC3	
FLAGS		dfrq3	0
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in	n	dpwr3	1
dp	y	dof3	0
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DISPLAY		dmm3	c
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		wbs	
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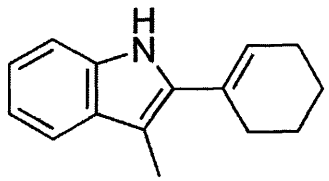

STANDARD CARBON PARAMETERS

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SAMPLE		DEC. & VT	
date	Oct 19 2004	dfrq	499.756
solvent	CDCl3	dn	H1
file	/data/slbuch/~	dpwr	34
	4dd/2_cyclohexylhy~	dof	0
	droxymethyl_3_meth~	dm	yyy
	ylindole_C_F.fid	dmm	w
ACQUISITION		dmf	10000
sfrq	125.676	dseq	
tn	C13	dres	1.0
at	0.869	homo	n
np	65536	DEC2	
sw	37718.1	dfrq2	0
fb	not used	dn2	
bs	16	dpwr2	1
ss	1	dof2	0
tpwr	58	dm2	n
pw	7.5	dmm2	c
d1	3.000	dmf2	10000
tof	615.5	dseq2	
nt	256	dres2	1.0
ct	128	homo2	n
alock	n	DEC3	
gain	not used	dfrq3	0
FLAGS		dn3	
il	n	dpwr3	1
in	n	dof3	0
dp	y	dm3	n
hs	nn	dmm3	c
DISPLAY		dmf3	10000
sp	-6304.1	dseq3	
wp	37718.1	dres3	1.0
vs	1299	homo3	n
sc	0	PROCESSING	
wc	250	lb	1.00
hzmm	2.97	wtfile	
is	500.00	proc	ft
rfl	6304.1	fn	131072
rfp	0	math	f
th	18		
ins	1.000	werr	
ai cdc ph		wexp	
		wbs	
		wnt